From:	Dourson, Michael [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BB29BF491D9A4C3AB569022BCD205A0A-DOURSON, MI]
Sent:	12/7/2017 8:18:08 PM
To:	Schlosser, Paul [Schlosser.Paul@epa.gov]
CC:	Barone, Stan [Barone.Stan@epa.gov]; Camacho, Iris [Camacho.Iris@epa.gov]; Beck, Nancy [beck.nancy@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]
Subject:	RE: "HEC99" for DCM

Paul

Thanks. The DDEF guidelines promote the use of PBPK modeling over straight comparisons of medium to upper limits, as you would expect, and as is approapriate. However, guidance exists for this situation and most folks that use DDEF type approaches pick 5%, probably because of stability issues as you suggest, but also on occasion because of physiological limits. For example, for boron we derived a DDEF based on 2 standard deviation decrease of Glomerular Filtration Rate (akin to 5%) because 3 SD of GFR was not compatible with life in pregnant women. Obviously, biology trumps math in such cases.

My point simple was to ask why 1%. Your response was a risk manager's response, not science. I will recommend that both 1% and 5% values be shown, or at least the ratio between the two be stated so that all of the tables can be understood to have a range in the MOE that is consistent with more than one risk management choice.

Stan is likely to be correct that the change is minor, but why should we suffer the constant critique of being overly conservative when the data show similar results with more reasonable assumptions?

Cheers!

Michael...

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From: Schlosser, Paul
Sent: Thursday, December 7, 2017 2:09 PM
To: Dourson, Michael <dourson.michael@epa.gov>
Cc: Barone, Stan <Barone.Stan@epa.gov>; Camacho, Iris <Camacho.Iris@epa.gov>
Subject: "HEC99" for DCM

Michael,
Cc: Stan, Iris

I think that what we did for the IRIS Tox Review was technically ***not*** a data-derived adjustment factor (DDAF). While one could back-calculate the corresponding factor, it was a direct calculation of the exposure concentration for which

99% of the population would have an internal dose below the BMDL from animal toxicity data. We did not calculate a median and then apply a DDAF.

Since the RfC is supposed to be the concentration expected to protect the human population, including sensitive sub-populations, it should nominally be a concentration that is protective of 100% of the population. However, the statistical analysis of the HEC distribution was expected to be unstable beyond 99%. At the time the analysis was being conducted, the concern was that the population-PBPK model did not adequately characterize the distribution for the entire population. For example, the specific age-range evaluated was 6 months to 80 years, so infants and people above 80 were not explicitly addressed. Metabolic activity for 0-6 months of age is much more uncertain, among other things. So the choice of 99% was a practical limit between using the population-PBPK model and covering 100% of the population, given that we already knew the parameter distribution didn't cover 100%.

To go beyond this, you'd need to get in touch with NCEA management, since we're going into details of the IRIS Tox Review, not OPPT's assessment.

Regards.
-Paul

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